

Clinico-pathological conference

Premature bullous pulmonary damage in AIDS

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Case report (Dr R F Miller)

A 31 year old Caucasian man was admitted to this hospital for investigation of fever, progressive weight loss and cavitating lesions on his chest radiograph. The patient was a business man, he was homosexual and denied intravenous drug abuse. He smoked 30 cigarettes per day and drank 2 units of alcohol per week.

His past medical history began in 1977 when he suffered from rectal gonococcus. In 1984 he developed oral candidiasis. Later on in 1986 he requested an HIV test. Following counselling he was found to be HIV-1 antibody positive. At this time he had further oral candidiasis and developed persistent generalised lymphadenopathy. In April 1988 *Giardia lamblia* was isolated in his stool. Because of persistent oral candidiasis he was commenced on ketoconazole, and zidovudine was also begun. In July of that year he presented with a 3-week history of fever, exertional dyspnoea and a non-productive cough. His chest radiograph was typical for *Pneumocystis carinii* pneumonia so bronchoscopy was not performed and the patient was treated with oral high-dose co-trimoxazole. He made a rapid recovery, complicated by the development of a severe skin rash after 10 days therapy. He completed treatment with nebulised pentamidine. Following discharge from hospital he recommenced zidovudine and received intermittent nebulised pentamidine prophylaxis.

He re-presented in September 1988 with further fever and cough associated with pleuritic pain, together with generalised myalgia. A sample of sputum, expectorated spontaneously, was negative for bacteria and acid- and alcohol-fast bacilli (AAFB). Culture of the sputum was also negative. His chest radiograph at that time (fig 1) showed an area of consolidation in the right upper zone. Within this area were several cavities. Despite the atypical presentation he was treated empirically for presump-

tive *Pneumocystis carinii* pneumonia with nebulised pentamidine. After 2 weeks treatment there had been no response, so the patient proceeded to fibre-optic bronchoscopy. At bronchoscopy the endobronchial appearances were normal. Transbronchial biopsy was attempted but was unsuccessful. Broncho-alveolar lavage fluid was smear-positive for AAFB. In addition cytoplasmic inclusions were seen and thought to represent cytomegalovirus infection. Culture of the lavage fluid, however, revealed no evidence of cytomegalovirus, and atypical mycobacteria were seen, thought possibly to be *Mycobacterium kansasii*. A sample was sent to the reference laboratory but was lost. In the light of the broncho-alveolar lavage findings, the patient commenced quadruple therapy with rifampicin, isoniazid, ethambutol and pyrazinamide. The patient's fever persisted and in view of the atypical mycobacteria, clofazimine was added with rapid lysis of fever. At

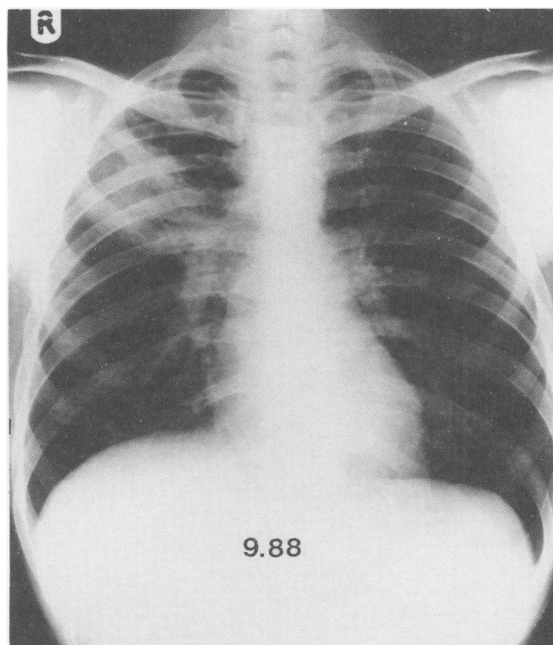


Fig 1 Chest radiograph showing an area of consolidation in the right upper zone, within this are several small cavities.

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this time the patient complained of poor memory. Investigations, including CT of the head, were normal.

The patient remained well until January 1989 when he was admitted with a 2-week history of poorly localised colicky abdominal pain and diarrhoea, passing between 12–15 watery stools per day. The patient had not been taking any prophylaxis against *Pneumocystis carinii* but had continued his treatment with rifampicin, isoniazid, ethambutol, pyrazinamide and clofazimine, together with ketoconazole and zidovudine. On examination his skin had a red tinge. This was attributed to being a side effect of the clofazimine. It was noted that his weight had increased by 15 kg since discharge from hospital the previous autumn. Culture of his stool revealed cryptosporidia. The patient's symptoms slowly settled and he received symptomatic treatment with loperamide. He represented in May 1989 with further intermittent fever, cough and exertional dyspnoea. He had further watery diarrhoea, passing up to 10 stools per day. His clofazimine had been stopped because of the skin discolouration, and fluconazole had been substituted for the ketoconazole. In addition he had been taking Fansidar (pyrimethamine and sulphadoxine) once weekly. Investigations showed a haemoglobin of 14 gm/dl with an MCV of 104 fl, white cell count $2.0 \times 10^9/l$ (lymphocytes $0.5 \times 10^9/l$). Stool culture on several occasions revealed cryptosporidia together with adenovirus. Arterial blood gases drawn whilst

breathing room air were normal, and a chest radiograph (fig 2) showed a right apical bulla. The haematological abnormalities were attributed to the zidovudine, which was discontinued. Clofazimine was recommenced and in order to treat the cryptosporidium infection, spiramycin by mouth was given. On this regime the patient's fever settled, the diarrhoea resolved, and an attempt was made to restart zidovudine at a low dose. This produced further neutropenia and so was stopped. Throughout this period the patient steadily lost weight, dropping from 62 kg to 53 kg over 6 weeks. In an attempt to stimulate weight gain, megestrol acetate (a progestagen) was commenced. At this stage the patient was transferred to us for further investigation.

On admission to this hospital the patient was cachectic, weighing 52 kg, he had marked seborrhoeic dermatitis of the face. The mucosae were pale and there was no evidence of cutaneous or palatal Kaposi's sarcoma. Lymphadenopathy was not detected. The patient was pyrexial, 38.2°C . In the chest there were scattered crackles but no focal abnormalities. Examination of the abdomen and central nervous system revealed no abnormalities, in the cardiovascular system marked postural hypotension was detected. Investigations showed haemoglobin 11.9 gm/dl with an MCV of 102 fl, white blood count

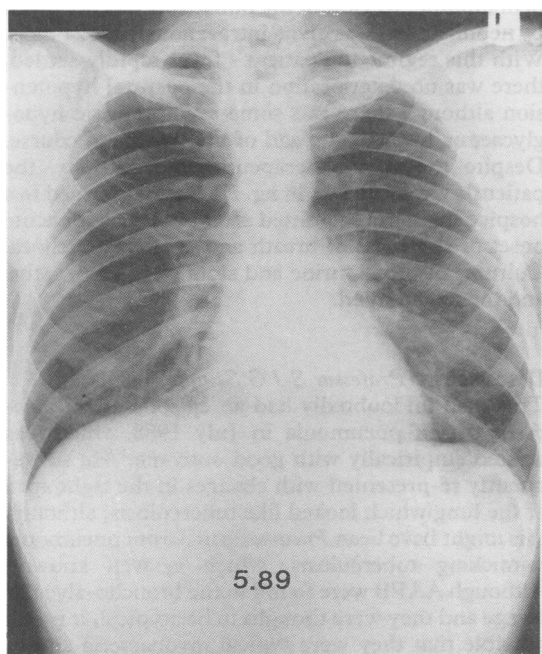


Fig 2 Chest radiograph showing a right apical bulla.

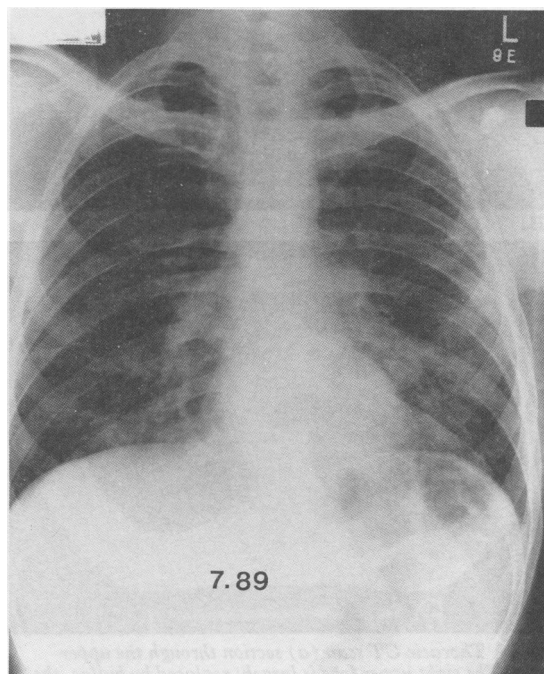


Fig 3 Chest radiograph showing that the right apical bulla has increased in size and that there is now a small left apical bulla. Both lung fields are diffusely abnormal with soft interstitial infiltrates.

$1.8 \times 10^9/l$ (78% neutrophils), platelet count normal, ESR 44 mm in the 1st hour. He was hyponatraemic, sodium = 125 (normal = 137–145) mmol/l, hypocalcaemic, calcium = 1.69, corrected calcium = 2.09 (normal = 2.20–2.60) mmol/l, and hypoalbuminaemic, albumin = 20 (normal = 35–53) gm/l. Potassium, creatinine and urea were normal. Liver function tests showed a normal bilirubin and alkaline phosphatase, AST was elevated at 88 (normal = 11–55) IU/l. He was hepatitis B surface antigen, anti-hepatitis B core, and hepatitis B e antigen positive, his syphilis serology was negative. Multiple blood cultures were negative, and samples of stool revealed cryptosporidia only. AAFB were not detected in blood, stool or urine samples. An ultrasound examination of the abdomen revealed splenomegaly only, lymphadenopathy was not detected and the liver was of normal size and echogenicity. In view of the postural hypotension and hyponatraemia a short synacthen test was carried out to exclude adrenocortical failure. Serum cortisol

before injection of synacthen was 489 nmol/l, and following injection of ACTH was 870 nmol/l (normal response > 150 nmol/l rise). The autonomic reflexes assessed non-invasively were normal.

Arterial blood gases drawn breathing room air revealed $PO_2 = 11.2$ (normal = 12–15) KPa, $PCO_2 = 3.9$ (normal = 4.5–5.3) KPa. A chest radiograph (fig 3) showed further enlargement of the right apical bullae. In addition both lung fields were diffusely abnormal with soft interstitial infiltrates. CT of the thorax was performed (fig 4); this showed that the right upper lobe was largely replaced by bullae. In addition there were multiple smaller bullae in the left upper lobe. There was a patchy diffuse increase in attenuation throughout both lungs. This was associated with bronchial wall thickening. In view of the finding of the bronchial wall thickening the patient proceeded to bronchoscopy in order to confirm a diagnosis of *Pneumocystis carinii* pneumonia. At bronchoscopy the endobronchial appearances were normal, broncho-alveolar lavage was performed and organisms of *Pneumocystis carinii* were seen. No AAFB, CMV nor bacteria were identified, and subsequent culture of the lavage was negative.

In view of the previous isolation of an atypical mycobacterium, thought to be *M. kansasii* the patient was commenced on rifampicin and ethambutol, together with amikacin. Fluconazole was recommended and fludrocortisone was given in order to ameliorate the postural hypotension. The *Pneumocystis carinii* pneumonia was treated with pentamidine. In view of the bullae this was not given by nebuliser but was given intravenously for 21 days. With this regime the patient's fever rapidly settled, there was no deterioration in the postural hypotension although there was some asymptomatic hypoglycaemia towards the end of the treatment course. Despite the above therapeutic interventions, the patient's weight fell to 48 kg. He was discharged to a hospice but was readmitted after 10 days with acute onset of shortness of breath and profuse diarrhoea. Cultures of blood, urine and stool were all negative and the patient died.

Discussion (Professor S J G Semple)

This man undoubtedly had an episode of *Pneumocystis carinii* pneumonia in July 1988 which was treated empirically with good outcome.¹ He subsequently re-presented with changes in the right apex of the lung which looked like tuberculosis, although this might have been *Pneumocystis carinii* pneumonia mimicking tuberculosis, which is well known.² Although AAFB were found in the broncho-alveolar lavage and they were thought to be atypical, it is still possible that they were typical mycobacteria and in favour of that was the fact that the chest radiograph

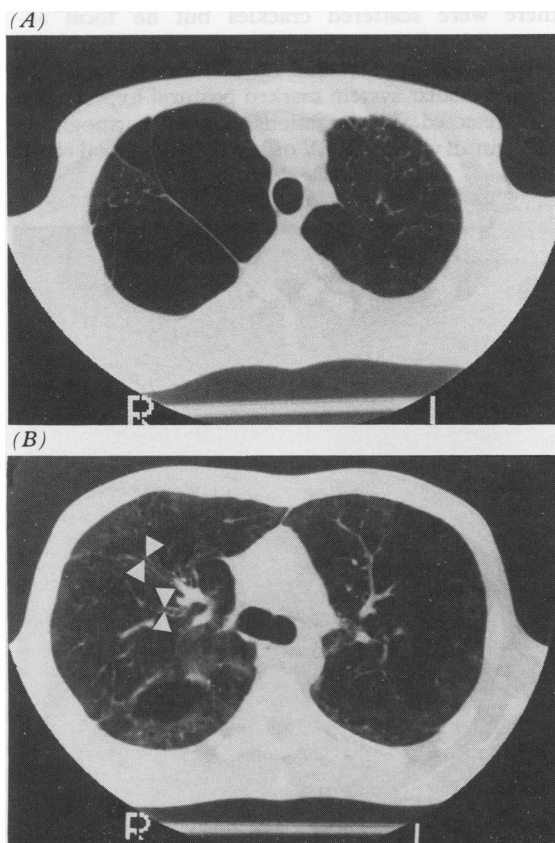


Fig 4 Thoracic CT scan (a) section through the upper lobes. The right upper lobe is largely replaced by bullae, the left upper lobe contains many smaller bullae. (b) section at the level of the carina showing patchy increase in attenuation in both lungs, in addition there is bronchial wall thickening (arrows).

cleared on therapy. If this had been purely atypical infection there would be several things about it which would be uncharacteristic. Firstly, atypical mycobacterial infection in HIV positive patients does not usually produce marked consolidation, it is usually a generalised disease and if it does occur in the lung it produces mediastinal lymphadenopathy, rarely progressive thick-walled cavitary destructive changes are seen.³ So, for atypical mycobacteria this behaved atypically and it may have been due entirely to *Pneumocystis carinii* pneumonia or he may have had *Mycobacterium tuberculosis* responsive to chemotherapy—as one would expect in an HIV positive patient.

There are many causes of multiple thin-walled cysts,⁴ including several infections, notably staphylococcal pneumonia. The particular appearances of the bullous changes seen in this case are typical of the abnormalities reported in HIV positive patients^{5,6} and have been termed "premature emphysema". In this condition the changes seen on the chest radiograph and the CT scan are similar to those which occur in the general ageing population.

The cause of premature bullous damage in AIDS is not known. Predisposing factors or possible causes include recurrent or prior infection, *Pneumocystis carinii* pneumonia, intravenous drug abuse, cigarette smoking and a possible direct cytotoxic effect on HIV on the lung.^{7,8} In one study,⁶ bullous damage, occurring predominantly in the apical and cortical areas of the lungs was seen on the CT scans of 42% of 55 patients with AIDS and also in 16% of 50 HIV negative neutropenic patients with acute leukaemia. The average age of the patients was 37 years and the changes seen could not be attributed to previous cigarette smoking or intravenous drug abuse. Both the AIDS and leukaemia patients with bullae were significantly more likely to have had previous or recurrent pneumonia than those without bullae. Thirteen per cent of the patients in this study had no past history of pulmonary infection of any kind, which raises the possibility of other predisposing factors. Premature emphysema had been associated with intravenous drug abuse long before the advent of AIDS.⁹

In another study,⁵ 8 (20%) of 40 patients with *Pneumocystis carinii* pneumonia had cystic changes on the chest radiograph, seven of the eight patients had AIDS, and the other patient had been immunosuppressed with steroids. In the same study 16 patients aged under 40 years also had cysts on the chest radiograph, 10 of the 16 patients were intravenous drug abusers (only one was HIV positive). In all the patients the cystic changes were seen in the upper lobes; CT was performed in several patients and showed the cystic changes in the intravenous drug abusing patients to be localised in the periphery of the lungs and in the patients with *Pneumocystis*

carinii pneumonia and AIDS to be scattered throughout the lungs.

Laboratory studies have demonstrated a direct cytotoxic effect of HIV on pulmonary macrophages. The macrophages release elastase, which is a key factor in the development of pulmonary emphysema.¹⁰ Alternatively, the rôle of HIV may be much more indirect creating conditions within the lung that predispose to infection by another organism, such as *Pneumocystis carinii*, and so cause a long period in which many activated and injured macrophages reside in the lung and release destructive elastase. Another potential contributory factor might be nebulised pentamidine;¹¹ use of this drug has been associated with the development of thin-walled apical bullae. In this patient the prior history of *Pneumocystis carinii* pneumonia together with his heavy cigarette intake and prior use of nebulised pentamidine may have been factors contributing to the development of the bullous changes.

When CT was performed in this patient it showed not only the extensive right apical bullous changes but also multiple bullae throughout both the lungs. In addition changes of bronchial wall dilatation/thickening were demonstrated, indicating *Pneumocystis carinii* pneumonia.¹²

The question arises as to why he had a persistent fever, steadily lost weight and was anaemic and neutropenic. One possibility would be that he had a disseminated mycobacterial infection, with either *Mycobacterium avium-intracellulare* complex or *Mycobacterium kansasii*; against a disseminated infection was the isolating of AAFB on only one occasion from one body site, and then multiple negative cultures. An alternative diagnosis to explain the symptoms would be a disseminated lymphoma; against this the absence of lymphadenopathy on examination, and on abdominal ultrasonography and thoracic CT. A bone-marrow aspirate and trephine were not performed but might have helped evaluate these two possibilities. The chronic diarrhoea due to cryptosporidia would also have contributed to his malnutrition and weight loss. The terminal event was probably a further episode of *Pneumocystis carinii* pneumonia, despite the recent successful course of IV pentamidine.

Clinical diagnosis

- (1) *Pneumocystis carinii* pneumonia
- (2) Premature bullous emphysema
- (3) Cryptosporidial diarrhoea
- (4) Atypical mycobacterial infection

Pathology (Dr S Lucas)

Macroscopically this man was cachectic and I wondered if he had an Addisonian tinge. In the lungs the

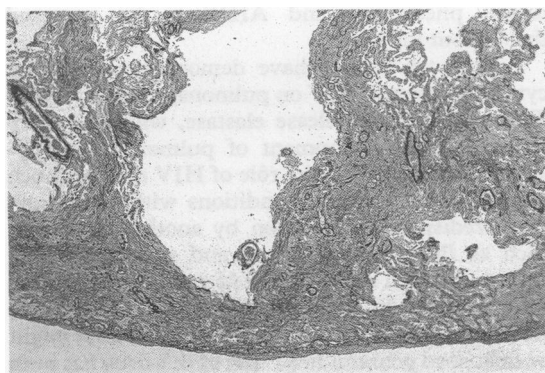


Fig 5 Lung subpleural bulla showing thin fibrous septae. Elastic van Gieson.

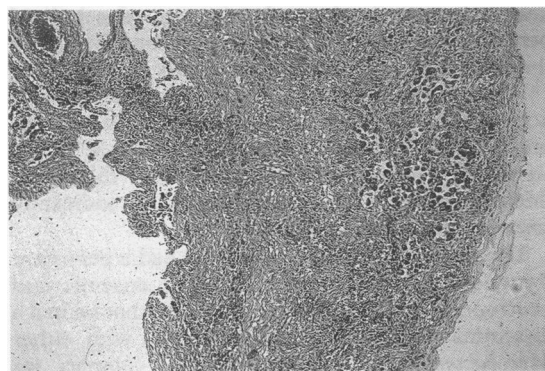


Fig 6 Wall of bulla; no necrosis or *Pneumocystis carinii* pneumonia under the pleura. Alveoli contain abundant CMV inclusions.

right upper and left upper lobes contained airfilled bullae. These bullae were up to 5 cm in diameter. There was no associated pleural scarring, nor was there scarring around the bullae; they were just holes within the lung. Within the rest of the lung there was consolidation but no necrosis. The heart was larger than normal and it was certainly flabby and pale. The gut, liver, kidneys, pituitary and thyroid all look quite normal. The spleen was congested. There were some small abdominal lymph nodes of normal appearance. The adrenals appeared a little atrophic, but there was no focal lesion evident. The brain weighed 1600 g and was of normal appearance on the cut slices. There was no evidence of a deep vein thrombosis.

Histopathological examination showed that the lungs were very abnormal. In both bases there were changes of adult respiratory distress syndrome with hyaline membrane formation, *Pneumocystis carinii* organisms were seen throughout the lung and next to but not within the cavities. The bullae were not associated with caeseation nor granuloma formation. They were simply holes in the lungs surrounded by

thin walls of fibrous tissue and ran right up to the pleural edge (fig 5). The cavities were lined with epithelial cells and one can see large numbers of CMV inclusions, so these bullae were colonised with CMV (fig 6).

Clearly these bullae were not congenital as they had been seen to progress. There were clearly not post-mycobacterial infection as one would expect to see either considerable fibrosis or residual necrosis. Even in somebody who had been treated adequately for a year; they are not likely to be due to cavitating *Pneumocystis carinii* pneumonia either; this pathological process begins with dense consolidation and granuloma formation which then necroses. The alternative explanation for those bullae is that they are non-specific emphysematous bullae. It is possible that they were secondary to cigarette smoking compounded by the HIV infection.

Within the heart there was no evidence of myocarditis. The myocardial fibres were rather large and had large nuclei, similar to those seen in congestive cardiomyopathy. The tongue had abnormal papillae with wart virus changes but no evidence of hairy leucoplakia. Fungal hyphae were demonstrated within the epithelium. The bowel had autolysed since the mucosa autolyses very quickly after death. Within the small bowel, however, there were multiple CMV inclusions. Cryptosporidia were not seen, these also autolyse and vanish very soon after death. The adrenals were small and there was evidence of inflammation of the cortico-medullary junction but there was no necrosis. At high power CMV inclusions were seen, so he clearly had a CMV adrenalitis. The tests were atrophic. The brain showed evidence of mild HIV-encephalopathy with microglial nodules in the cortex, cerebellum and in the basal ganglia.

Pathological diagnosis

- (1) Apical bullous lung disease (HIV-related).
- (2) Cytomegalovirus colonisation; bowels, adrenals, lungs.
- (3) *Pneumocystis carinii* pneumonia with adult respiratory distress syndrome.
- (4) HIV-encephalopathy.

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